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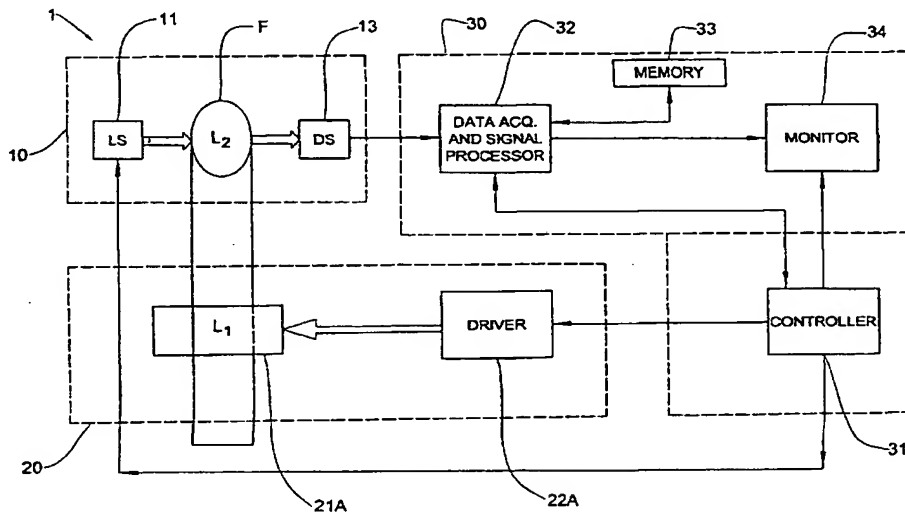
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(54) Title: **A METHOD AND DEVICE FOR MEASURING THE CONCENTRATION OF GLUCOSE OR OTHER SUBSTANCES IN BLOOD**



(57) Abstract: A method and device for optical measurements are presented for determining the concentration of a substance in patient's blood. Optical measurement sessions are applied to a measurement location in a blood containing medium during certain time period. The optical measurements include illumination of the measurement location with incident light of at least one selected wavelength, detection, at each measurement session, of at least two light responses of the medium characterized by at least two different polarization states of detected light, respectively, and generation of data representative thereof. Measured data so obtained is in the form of at least two time variations of the light responses of the medium characterized by different polarization states of detected light, respectively, a relation between the time variations being indicative of the concentration of the substance in blood.

WO 01/96872 A2

24

- 2 -

Various techniques have been developed aimed at facilitating the measurement of the concentration of glucose in a patient's blood. These techniques are disclosed, for example, in the following publications:

- 5       - "*Blood Analysis: Noninvasive Methods Hover on Horizon*", K. Robinson, Biophotonics International, May/June 1998;
- "*Glucose- and Blood-Monitoring Systems Vie for Top Spot*", Susan M. Reiss, Biophotonics International, May/June 1997;
- "Optical Glucose Sensing in Biological Fluids: and Overview", Roger J. McNichols, Gerard Cote, Journal of Biomedical Optics, January 2000, Vol. 5. No. 1, pp. 5-16; and
- 10       - US Patents Nos. 5,209,231; 5,398,681; 5,448,992; 5,687,721; 5,692,504; 5,551,422; 5,676,143; 5,533,509; 5,687,721; 4,901,728.

Most of the above techniques are based on the known phenomenon consisting in that glucose, being an optically active medium, rotates polarized light, and the  
15 higher the concentration of glucose, the greater the rotation.

According to all prior art techniques, measurements are applied to a blood flow containing medium during the state of normal blood flow, and the measured signals are pulsatile-related signals.

A different technique for measuring various blood-related parameters has  
20 been developed and disclosed in WO 99/66322, assigned to the assignee of the present application. This technique utilizes the so-called occlusion-release mode, wherein over-systolic pressure is applied to a patient's blood perfused fleshy medium so as to create the state of blood flow cessation at a measurement location. Optical measurements are applied during a time period including cessation time, during  
25 which the state of blood flow cessation is maintained, and time dependencies of "non-pulsatile" light responses of the medium are determined for at least two wavelengths of incident radiation. This technique enables to significantly enhance the light response signal, as compared to that obtained with the pulse oximetry.

- 4 -

however, measurements are carried out in a manner to detect at least two light responses of the medium characterized by two different states of polarization, respectively, and to measure time variations of the light responses. To this end, pressure is applied to a location on the blood containing medium (e.g., over-systolic pressure applied to the patient's blood perfused fleshy medium, in the case of non-invasive measurements), and the measurement location to which the optical measurement sessions are applied, is located downstream of the pressurized location with respect to the blood flow direction. The application of pressure causes artificial change in the velocity of blood, namely, causes the state of blood flow cessation at a location downstream of the pressurized location. The artificial change in the blood results in the aggregation of red blood cells (Rouleaux effect) with time-varying shape and size of aggregates. At the state of the blood flow cessation, when there is actually no blood flow, no shear forces prevent the erythrocytes' aggregation process. Hence, the light response (transmission or reflection) of the blood perfused fleshy medium at the state of the blood flow cessation can be considered as the time dependence of scattering in a system with growing scatterers.

Glucose, being the main optically active substance in blood, influences the optical characteristics of scattered and partly absorbed radiation in a complicated manner. More specifically, glucose introduces changes in the ratio of refraction indices of erythrocytes and surrounding plasma, and introduces spectrally dependent optical rotation (rotary dispersion). These factors lead to dynamic changes in the state of polarization, in particular the polarization or depolarization degree, under the condition of kinetic changes in the aggregates in the case of periodical application of occlusion (occlusion-release sessions).

Dynamic multiple scattering increases the optical path of radiation scattered from a blood sample and, consequently, the angle of rotation of polarization of incident light. Additionally, it is known that the state of polarization of incident light affects the light scattering properties (via the Stokes parameters). Thus, the results of the transmission or reflection measurement will be governed by the state of polarization of the incident light. This means that any change in the relative refraction

- 6 -

Thus, the method consists of determining quantitative relationship between the kinetics of changes in polarized light (while at the "flow-stop" mode) passed through an absorbing and scattering medium that contains a certain concentration of scattering affecting substance, and the concentration of this substance. The medium under measurements is the patient's blood perfused fleshy medium, e.g., his finger, when dealing with *in vivo* measurements, or a suspension of RBC in cuvette, in the case of *in vitro* measurements.

The method consists of two stages: At the first stage, correlation between the concentration of a substance (glucose) and a predefined, non-dimensional parameter,  $R$ , is measured. This measurable parameter  $R$  is indicative of some kind of a mathematical relation between the two opto-kinetic signals (occlusion curves), generated by scattering, absorption and polarization changes, occurring during the state of blood aggregation.

For example, the parameter  $R$  may present a parametric slope (tangent of the angle of inclination) of a curve representative of multiple scattered polarized light. Graphically, this is an inclined line in coordinates  $(T_1-T_2)$ , or  $(\log T_1-\log T_2)$ , wherein  $T_1$  is the light response of the medium with one state of polarization (e.g., linearly polarized light), and  $T_2$  is the light response of the medium with another state of polarization. These different light responses may, for example, be obtained by illuminating the medium with incident light of the same wavelength but different polarization states. Since this curve is indicative of the kinetic curves reflecting the complete attenuation of the polarized and unpolarized light, respectively, it actually presents a curve of the multiple scattered polarized light.

Another possible example of such a parameter  $R$  may be the degree of depolarization of the collected light, which is the function of time and can be calculated as follows:  $(T_1-T_2)/(T_1+T_2)$ . This function is different for different wavelengths of incident light.

The measurable parameter  $R$  (e.g., parametric slope of the curve  $T_1(T_2)$  or degree of depolarization) is indicative of the glucose concentration in the blood under measurements. To determine the glucose concentration  $C_{gl}$ , reference data in the form

- 8 -

within a measurement location downstream of the location of application of pressure, and maintaining said state during a certain cessation time;

- performing optical measurement sessions within a time period including said certain cessation time, the optical measurements including illumination of the measurement location with incident light of at least one selected wavelength, detection, at each measurement session, of at least two light responses of the medium characterized by at least two different polarization states of detected light, respectively, and generation of data representative thereof;
- obtaining measured data in the form of at least two time variations of the light responses of the medium, a relation between the time variations being indicative of the concentration of the substance in blood.

According to yet another aspect of the present invention, there is provided a method for determining the concentration of a substance in a patient's blood, the method comprising the steps of:

- providing reference data indicative of a preset measurable parameter as a function of values of said concentration;
- creating a state of blood flow cessation within a measurement location in a blood flow containing medium, and maintaining said state during a certain cessation time;
- performing optical measurement sessions within a time period including said certain cessation time, the optical measurements including illumination of the measurement location with incident radiation of at least one selected wavelength, detection, at each measurement session, of at least two light responses of the medium characterized by at least two different polarization states of detected light, respectively, and generation of measured data representative thereof;
- utilizing the measured data for obtaining measurement results in the form of at least two kinetic curves of the light responses of the medium as

- 10 -

- utilizing the calculated value and said reference data for determining the concentration of the substance in the patient's blood.

To detect light beams with different polarization states, one of the following implementations is possible:

- 5       (1) The medium (at the measurement location) is illuminated with two beams of incident radiation having different polarization states (e.g., polarized and unpolarized light), and a specific polarization filtering, common for both beams of the incident light, is applied at the detection side.

To this end, the illumination unit may comprise two light sources (e.g., sequentially operable) generating two light beams, respectively, and comprises either  
10 a single polarizer mounted stationary in the optical path of one of the generated beams, or two polarizers with different orientations of their planes of preferred polarization mounted in the optical paths of the two beams, respectively. Alternatively, a single light source can be utilized to generate two timely separated  
15 beams of incident light. In this case, a polarizer of the illumination unit is shiftable between its operative and inoperative positions, being in and out of the optical path of the incident beam, respectively.

As for the detection means, it comprises a detector unit equipped with an analyzer mounted stationary in the optical path of light returned from the medium  
20 (e.g., transmitted), provided the plane of preferred polarization of the analyzer is specifically oriented with respect to that of the polarizer(s) of the illumination unit.

- (2) The medium is illuminated with an incident beam having a predefined polarization state, and different polarization filtering is applied at the detection side with respect to two spatially separated light components of a transmitted (or  
25 reflected) beam, respectively. For this purpose, the illumination unit comprises a single light source emitting a beam of light, and a single polarizer mounted in the optical path of the emitted beam. The detection means comprises a pair of detector units and either two differently oriented analyzers mounted in front of the detector units, respectively, or a single analyzer mounted in front of one of the detector units  
30 only.

- 12 -

- 5       - a measurement device that comprises a pressurizing assembly operable to apply over-systolic pressure to a location on the patient's blood perfused fleshy medium, so as to create a state of blood flow cessation at a measurement location in the medium located downstream of the location of the application of pressure; and comprises a measuring unit operable to perform optical measurement sessions to said measurement location, the measuring unit comprising an illumination system and a light collection/detection system which are operable so as to detect at least two light responses of the medium characterized by at least two different polarization states of detected light, respectively, and generate measured data representative thereof; and
- 10       - a control unit connectable to the measurement device for selectively operating said measuring unit and said pressurizing assembly, such that the state of blood flow cessation is maintained during a certain cessation time being insufficient for irreversible changes in the fleshy medium, and the optical measurement sessions are performed within a time period including said cessation time, the control unit being responsive to said measured data to determine time variations of said at least two light responses of the medium corresponding to at least two different polarization states of the detected light, and analyze the time variations for determining a preset parameter measured as a relation between the time variations, and determining the concentration of said substance using reference data indicative of the preset measurable parameter as a function of values of the substance concentration.

25       According to yet another aspect of the present invention, there is provided a measurement device for performing non-invasive optical measurements for determining the concentration of a substance in a patient's blood, the device comprising

- 30       - a pressurizing assembly operable to apply over-systolic pressure to a location on the patient's blood perfused fleshy medium, so as to create a

- 14 -

Fig. 4 graphically illustrates the experimental results of the operation of the device of Fig. 1A (*in vivo*), in the form of two time variations of the light responses of the medium corresponding to two different polarization states of detected light; respectively;

5 Fig. 5A graphically illustrates the relation between the two curves in Fig. 4 in logarithmic coordinates for the same value of actual glucose concentration, used for the determination of a parametric slope;

Fig. 5B illustrates different graphs with different parametric slopes corresponding to different values of the concentrations of glucose, respectively;

10 Fig. 6 illustrates a calibration curve obtained from the graphs of Fig. 5B, and used for determining the level of glucose in the patient's blood; and

Fig. 7 illustrates the correlation between the measurements of glucose concentration obtained by the measurement device according to the invention and by the standard glucometer "Elite".

## 15 DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

Referring to Fig. 1A, there is illustrated a measurement system 1, according to one embodiment of the invention. The system is intended for *in vivo* optical measurements of patient's blood parameters utilizing an occlusion-release-based technique. The system 1 comprises a measurement device, which is applied to the patient's finger F (constituting a blood containing medium or BCM) and a control unit.

The measurement device comprises such main constructional parts as a measuring unit (or optical sensor), generally designated 10, and a pressurizing assembly (the so-called "occluder") 20. Control unit 30 is connectable to the measurement device, namely, to the measuring unit 10 and to the occluder 20 to selectively operate each of them. The occluder 20 is operable by the control unit 30 to apply over-systolic pressure to a first location  $L_1$  on the finger F and maintain the pressure during a certain time period (cessation time). Such application of the over-systolic pressure at the location  $L_1$  results in the creation of the state of blood

- 16 -

For the purposes of the present invention, the construction and operation of the measuring unit (i.e., illumination and detection systems) is aimed at providing the detection of at least two time variations of light responses (transmission) of the BCM corresponding to at least two different polarization states of detected light, respectively. To this end, the measuring unit is operable to perform at least two timely separated measurement sessions, each including the illumination of the measurement location with at least one wavelength of incident light, and the detection of light responses of the medium characterized by different polarization states of the detected light, respectively. Figs. 2A-2E illustrate different possible examples of the implementation of the illumination and detection systems.

According to the examples of Figs. 2A-2C, the difference in the polarization states of the detected light beams is introduced at the illumination stage, and consequently, two incident light beams are timely separated. In the examples of Figs. 2D and 2E, this difference is introduced by performing polarization filtering at the light collection/detection stage, and therefore, a single incident light beam can be generated for performing two measurement sessions.

In the example of Fig. 2A, the illumination system 11 comprises an illuminator including two light sources or emitters  $E_1$  and  $E_2$  (e.g., LEDs) generating light beams  $B_1$  and  $B_2$ , respectively, and comprises a polarizer  $P_1$  installed in the optical path of one of the emitted beams – beam  $B_1$  in the present example. Thus, beams  $B_1'$  and  $B_2$  impinging onto the BCM are, respectively, polarized and unpolarized beams. Beams  $B_1$  and  $B_2$  have the same selected wavelength in the visual or near infrared spectra. The light sources  $E_1$  and  $E_2$  may be sequentially operated by the control unit, so as to provide time separation between the incident beams  $B_1'$  and  $B_2$ .

The detection system 13 comprises a detector unit  $D$  (e.g., photodetector) and an analyzer  $A$  mounted in the optical path of light ensuing from the BCM, namely beams  $B_1''$  and  $B_2''$  corresponding, respectively, to the incident beams  $B_1'$  and  $B_2$ . The analyzer  $A$  has a plane of preferred polarization oriented different from that of the polarizer  $P_1$ , being for example, orthogonal thereto. The detector unit  $D$  detects a

- 18 -

operational modes. The construction and operation of a retarder are known *per se*, and therefore need not be specifically described, except to note that the retarder may utilize a ferroelectric liquid crystal material (switchable), or a voltage dependent (tunable) liquid crystal (nematic) material.

5       The polarized light beam  $B_1'$  propagating towards the BCM passes through the retarder  $RT$ , which affects the orientation of the plane of polarization of the linearly polarized light. Light beam  $B_1''$  ensuing from the retarder  $RT$  propagates through the BCM producing an output light beam  $B_1'''$ , propagating towards the detection system 13. The latter comprises a single analyzer  $A$  having the plane of  
10 preferred polarization specifically oriented with respect to that of the polarizer  $P_1$ . Thus, light  $B_1''''$  ensuing from the analyzer  $A$  presents the light response of the medium to be detected by the detector unit. It should be understood, that in order to obtain the time dependencies of different light responses (i.e., corresponding to different polarization states of detected light), the illumination/detection session is  
15 repeated at least twice (i.e., at different moments of time), each session including two measurements with different polarization states of incident light, respectively.

According to the examples of Figs. 2D and 2E, the illumination system 11 comprises a single light emitter  $E_1$  and a single polarizer  $P_1$  in the optical path of emitted beam  $B_1$ . The detection system 13 comprises two detector units  $D_1$  and  $D_2$ ,  
20 and is capable of simultaneously (i.e., during the same measurement session) detecting light responses of different polarization states of light, respectively.

To this end, as shown in the example of Fig. 2D, one of the detector units ( $D_1$ ) is provided with the analyzer  $A_1$ , while the other detector unit ( $D_2$ ) is not. Thus, a polarized beam  $B_1'$  impinges onto the BCM. A transmitted beam  $B_1''$  partly passes  
25 through the analyzer  $A_1$  resulting in the light response  $B_1'''$  received by the detector  $D_1$ , while the other presents a light response  $B_1''$  of the medium directly received by the detector  $D_2$ . These light responses  $B_1'''$  and  $B_1''$  are characterized by different polarization states.

- 20 -

flow before the over-systolic pressure is applied. As shown, this state is characterized by a standard fluctuating value of the relative light transmission of blood. State **B** starts at the moment  $T_{start}$  (when the pressure is initially applied) and exists during a short period of time  $T_B$  (about 0.5sec) within which the over-systolic pressure is actually applied. Measurements taken during this time period should be disregarded, due to the unavoidable influence of motional and/or other artifacts causing non-monotonic fluctuations of the light transmission.

State **C** is a state of the temporary cessation of blood flow which lasts within a time period  $T_C$  between a moment determined as  $(T_{start} + T_B)$  and the moment  $T_{release}$ . During this period of time,  $T_C$ , the ascending curve (or descending curve depending on the incident wavelength) of relative light transmission of blood is observed. It reaches its maximum, and may last for about 2-5.5 sec (generally, from one second to several minutes).

It is appreciated that when over-systolic pressure is applied to any proximal part of the body, there is still sufficient space for the redistribution of blood between the exact area of the measurement (i.e., the measurement location, where the detector is located) and the adjacent areas in close proximity to the detector. For example, if the detector is located on a fingertip and over-systolic pressure is applied on the palm, there is enough space between the fingertip and the margin of the applied pressure to "squeeze" the blood flow from one location to another.

State **D** is a transitional state of blood flow which takes place after releasing the over-systolic pressure. This state starts with a slight delay  $T_d$  (approximately 0.5sec), i.e. at the moment determined as  $(T_{release} + T_d)$ . During the time period  $T_D$  of the duration of state **D**, the relative transmission of blood monotonously descends until it reaches values characteristic of the normal blood flow. Such a moment is marked as  $T_{end}$  in the drawing. The end of state **D**, and the beginning of state **E**, is detected when the changes of the light transmission become periodic and minimal (about 2%). State **E** is a state of normal blood flow, which is similar to state **A**.

According to the invented method of optical measurements, measured data is obtained in the form of at least two time variations (evolutions) of light response of

- 22 -

graphs  $G_1$  and  $G_2$  of Fig. 4. The graph  $CV$  is a substantially straight line, the tangent of the angle of inclination  $\varphi$  of this line with respect to the abscissa axis presents a parametric slope, constituting a measurable parameter  $R$ .

Fig. 5B shows a set of curves – five curves  $V_1$ - $V_5$  in the present example, presenting the experimental results of applying the technique of the present invention to blood samples with different known values of the concentration of glucose, i.e., 102mg/dl; 116mg/dl; 128mg/dl; 146mg/dl and 160mg/dl. It is evident that each of these curves is characterized by a different value of the parametric slope  $R$ , as compared to the others.

The graphs  $V_1$ - $V_5$  are used for preparing reference data in the form of a calibration curve  $C_{cal}$  shown in Fig. 6. The calibration curve is initially prepared either with respect to each specific patient at different conditions of the concentration of glucose, or with respect to various patients with different glucose concentrations in blood.

Utilizing the measured data illustrated in Fig. 5A ( $T_1(t)$  and  $T_2(t)$ ) obtained by applying the measurements of the present invention to the specific patient, and the calibration curve  $C_{cal}$  of Fig. 6, the glucose concentration  $C_g$  in the patient's blood can be determined. In this specific example, the parametric slope  $R$  is equal to 1.27, and, consequently, for the glucose concentration, we have:  $C_g=102\text{mg/dl}$ .

Fig. 7 illustrates the correlation between the measurements of glucose concentration obtained by the measurement device according to the invention and those obtained by the standard glucometer "Elite".

As indicated above, the measurable parameter  $R$  enabling the determination of the concentration of substance in blood by using a calibration curve may be the degree of depolarization in the detected light, i.e.,  $(T_1-T_2)/(T_1+T_2)$ , which is the function of time, and varies from wavelength to wavelength. It should be understood, although not specifically shown, that a corresponding calibration curve will be in the form of the degree of depolarization as the function of glucose concentration.

It should also be noted, although not specifically shown, that to increase the accuracy of measurements, each measurement session may include the illumination

- 24 -

**CLAIMS:**

1. A method of optical measurements for determining the concentration of a substance in a patient's blood, the method comprising the steps of:
  - performing optical measurement sessions within a certain period of time  
5 by illuminating a measurement location in a blood containing medium with incident light of at least one selected wavelength, detecting, at each measurement session, at least two light responses of the medium characterized by at least two different polarization states of detected light, respectively, and generating data representative thereof; and
  - 10 - obtaining measured data in the form of at least two time variations of the light responses of the medium, a relation between the time variations being indicative of the concentration of the substance in blood.
2. The method according to Claim 1, wherein said measurements are carried out non-invasively, said measurement location being located in the patient's blood  
15 perfused fleshy medium.
3. The method according to Claim 1, and also comprising the steps of creating a state of blood flow cessation at the measurement location and maintaining said state for a certain cessation time, said certain time period during which the optical measurement sessions are performed including said certain cessation time, the  
20 creation of the state of blood flow cessation including application of pressure to a location on the blood containing medium upstream of said measurement location with respect to the blood flow direction.
4. The method according to Claim 2, and also comprising the step of creating a state of blood flow cessation at the measurement location and maintaining said state  
25 for a certain cessation time being insufficient for irreversible changes in the fleshy medium, said certain time period during which the optical measurement sessions are performed including said certain cessation time, the creation of the state of blood flow cessation including application of over-systolic pressure to the patient's blood

- 26 -

12. The method according to Claim 6, wherein said relation between the time variations is a parametric slope of a curve, which is in the form of one light response as the function of the other.

13. The method according to Claim 6, wherein said relation between the time variations is degree of depolarization calculated as a ratio between the difference of light responses' intensities and their sum.

14. The method according to Claim 6, wherein the optical measurements during each of the measurement sessions comprises:

illuminating the medium with at least two incident beams having different polarization states, such as to produce at least two output light beams coming from the illuminated medium; and

directing the output light beams towards a detector unit through an analyzer whose plane of preferred polarization is specifically oriented with respect to that of the incident beams.

15. The method according to Claim 6, wherein the optical measurements during each of the measurement sessions comprises:

illuminating the medium with a beam of incident light having a certain state of polarization, such as to produce an output light beam coming from the illuminated medium; and

directing the output light beam towards two detector units, such that only one light component of the output light beam is directed towards a corresponding one of the detector units through an analyzer whose plane of preferred polarization is specifically oriented with respect to that of the incident beam, while the other light component of the output light beam is directly detected by the other detector unit.

16. The method according to Claim 6, wherein the optical measurements during each of the measurement sessions comprises:

illuminating the medium with a beam of incident light having a certain state of polarization, so as to produce an output light beam coming from the illuminated medium;

- 28 -

two light responses of the medium characterized by at least two different polarization states of detected light, respectively, and generation of measured data representative thereof;

- 5 (d) utilizing the measured data for obtaining measurement results in the form of at least two kinetic curves of the light responses of the medium as functions of time corresponding to the different polarization states of the detected light;
- (e) analyzing said at least two kinetic curves for calculating said certain measurable parameter indicative of relation between them; and
- 10 (f) utilizing the calculated value and said reference data for determining the concentration of the substance in the patient's blood.

19. The method according to Claim 18, wherein said substance is glucose.

20. The method according to Claim 18, wherein said at least one selected wavelength is in the range of visual or near infrared spectra.

- 15 21. The method according to Claim 18, wherein said reference data comprises a calibration curve obtained by applying steps (b) to (e) to blood containing media with different known values of the concentration of said substance.

22. The method according to Claim 18, wherein the measurements are performed *in vitro*.

- 20 23. The method according to Claim 18, wherein the measurements are performed *in vivo*.

24. The method according to Claim 23, wherein said measurement location is located at the patient's finger.

- 25 25. The method according to Claim 18, wherein said certain measurable parameter is a parametric slope of a curve, which is in the form of one light response as the function of the other.

26. The method according to Claim 18, wherein said certain measurable parameter is degree of depolarization calculated as a ratio between the difference of the light responses' intensities, and their sum.

- 30 -

- providing reference data indicative of a preset measurable parameter as a function of values of said concentration;
- applying over-systolic pressure to a location of the patient's blood perfused fleshy medium, thereby creating a state of blood flow cessation within a measurement location downstream of the location of application of pressure with respect to the blood flow direction, and maintaining said state of the blood flow cessation during a certain cessation time being insufficient for irreversible changes in the fleshy medium;
- performing optical measurement sessions within a time period including said certain cessation time, the optical measurements including illumination of the measurement location with incident light of at least one selected wavelength, detection, at each measurement session, of at least two light responses of the medium characterized by at least two different polarization states of detected light, respectively, and generation of data representative thereof;
- utilizing the measured data for obtaining measurement results in the form of at least two kinetic curves of the light responses of the medium as functions of time corresponding to the different polarization states of the detected light;
- analyzing said at least two kinetic curves for calculating said certain parameter indicative of relation between them, and
- utilizing the calculated value and said reference data for determining the concentration of the substance in the patient's blood.

31. A measurement system for determining the concentration of a substance in patient's blood, the system comprising:

- (i) a measurement device comprising a pressurizing assembly for applying pressure to a blood flow containing medium, so as to create a state of blood flow cessation at a measurement location in the medium downstream of the pressurized location with respect to the direction of blood flow; and a measuring unit for performing optical measurement sessions at

- 32 -

35. The system according to Claim 31, wherein the measurement location is located inside a flow cuvette through which the flow of patient's blood sample is drawn.

36. The system according to Claim 34, wherein the pressurizing assembly  
5 comprises a cuff for wrapping the patient's finger, squeezing of the cuff being operated by a drive coupled to the control unit.

37. The system according to Claim 31, wherein the pressurizing assembly comprises a peristaltic pump operated by a drive coupled to the control unit

38. The system according to Claim 32, wherein  
10 said illuminator is operable to produce two beams of light, and said polarizer unit comprises at least one polarizer accommodated in optical path of one of said two beams, thereby producing two incident beams of different polarization state, respectively, and producing two output beams coming from the illuminated medium;  
15 the collection/detection system comprises the single analyzer accommodated in optical path of the output light propagating towards the single detector unit.

39. The system according to Claim 32, wherein  
said illuminator is operable to produce two beams of light, and said polarizer unit comprises a polarizer accommodated in the optical path of each of said  
20 two beams, and a retarder accommodated in the optical path of each of said two beams and operable with different operational modes with respect to said two beams, the illuminator thereby producing two incident beams of different polarization states, respectively;  
the collection/detection system comprises the single analyzer accommodated  
25 in optical path of the output light propagating towards the single detector unit.

40. The system according to Claim 32, wherein  
said illuminator is operable to generate a beams of light, and said polarizer unit comprises a polarizer accommodated in optical path of the generated beam propagating towards the medium, thereby producing output light  
30 coming from the illuminated medium;

- 34 -

measured data to determine time variations of said at least two light responses of the medium corresponding to at least two different polarization states of the detected light, analyze the time variations for determining a preset parameter measured as a relation between the time variations, and determining the concentration of said substance using reference data indicative of the preset measurable parameter as a function of values of the substance concentration.

44. A measurement device for performing non-invasive optical measurements for determining the concentration of a substance in patient's blood, the device comprising:

- a pressurizing assembly operable to apply over-systolic pressure to a location on the patient's blood perfused fleshy medium, so as to create a state of blood flow cessation at a measurement location in the medium located downstream of the location of application of pressure, and to maintain said state during a certain cessation time being insufficient for irreversible changes in the fleshy medium; and
- a measuring unit operable to perform optical measurement sessions at said measurement location within a time period including said cessation time, the measuring unit comprising an illumination system and a light collection/detection system which are operable to detect, at each measurement session, at least two light responses of the medium characterized by at least two different polarization states of detected light, respectively, and generate measured data representative thereof, the measured data being indicative of time variations of said at least two light responses of the medium corresponding to at least two different polarization states of the detected light, a relation between said time variations being indicative of the concentration of said substance.

45. The device according to Claim 44, wherein said substance is optically active or scattering affecting substance.

46. The device according to Claim 45, wherein said substance is glucose.

- 36 -

the light collection/detection system comprises two detector units for detecting two spatially separated light components of the output light, two analyzers being accommodated in optical path of said two light components, respectively, propagating towards the detection units, the analyzers having  
5 different orientation of planes of preferred polarization.

52. The device according to Claim 44, wherein said relation between the time variations is a parametric slope of a curve, which is in the form of one light response as the function of the other.

53. The device according to Claim 44, wherein said relation between the time  
10 variations is degree of depolarization calculated as a ratio between the difference of light responses' intensities and their sum.

2/10

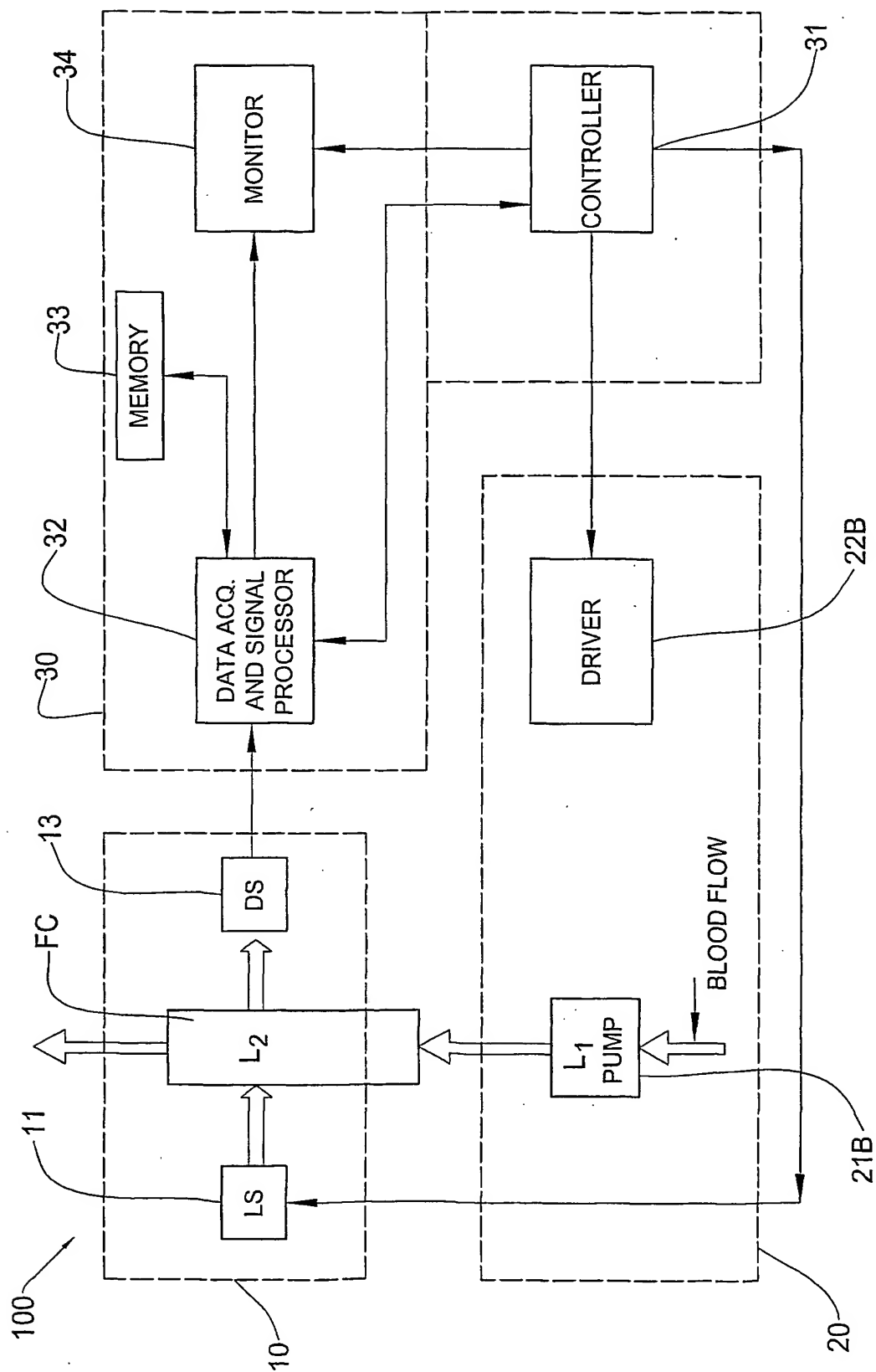


FIG. 1B

4/10

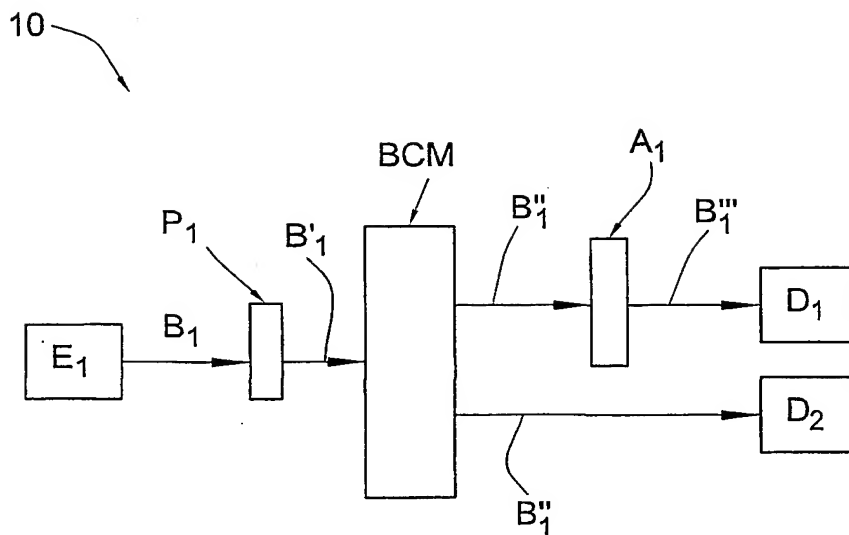


FIG. 2D

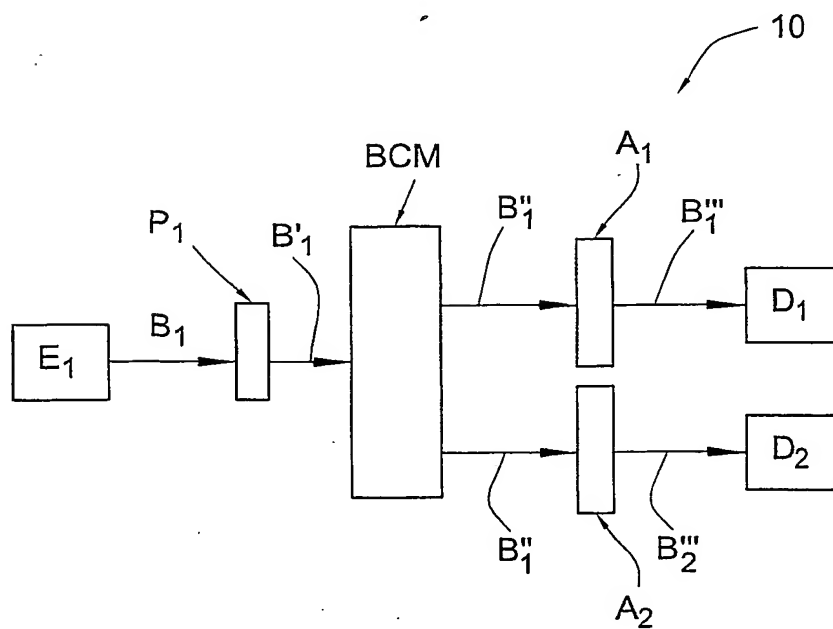


FIG. 2E

6/10

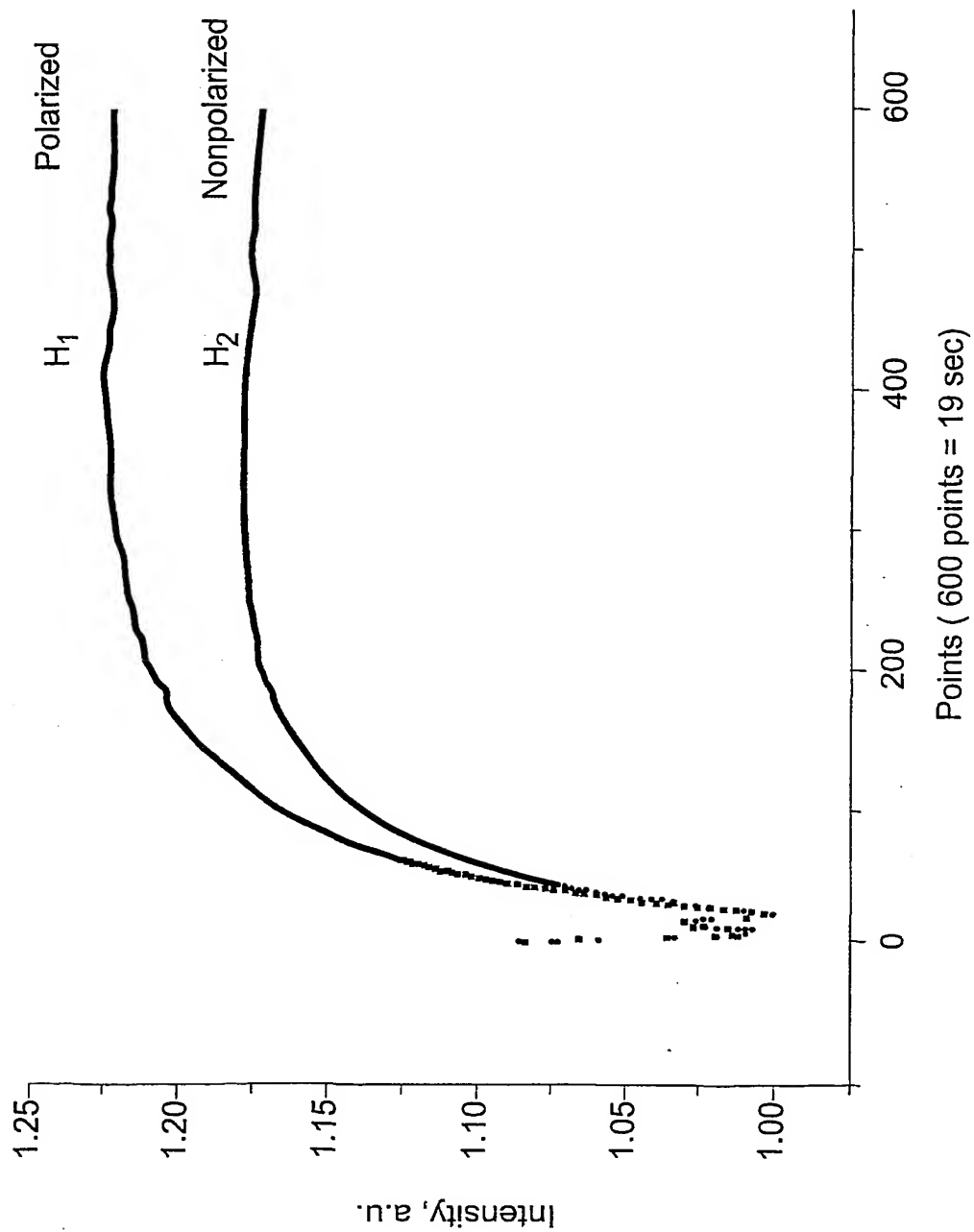


FIG. 4

8/10

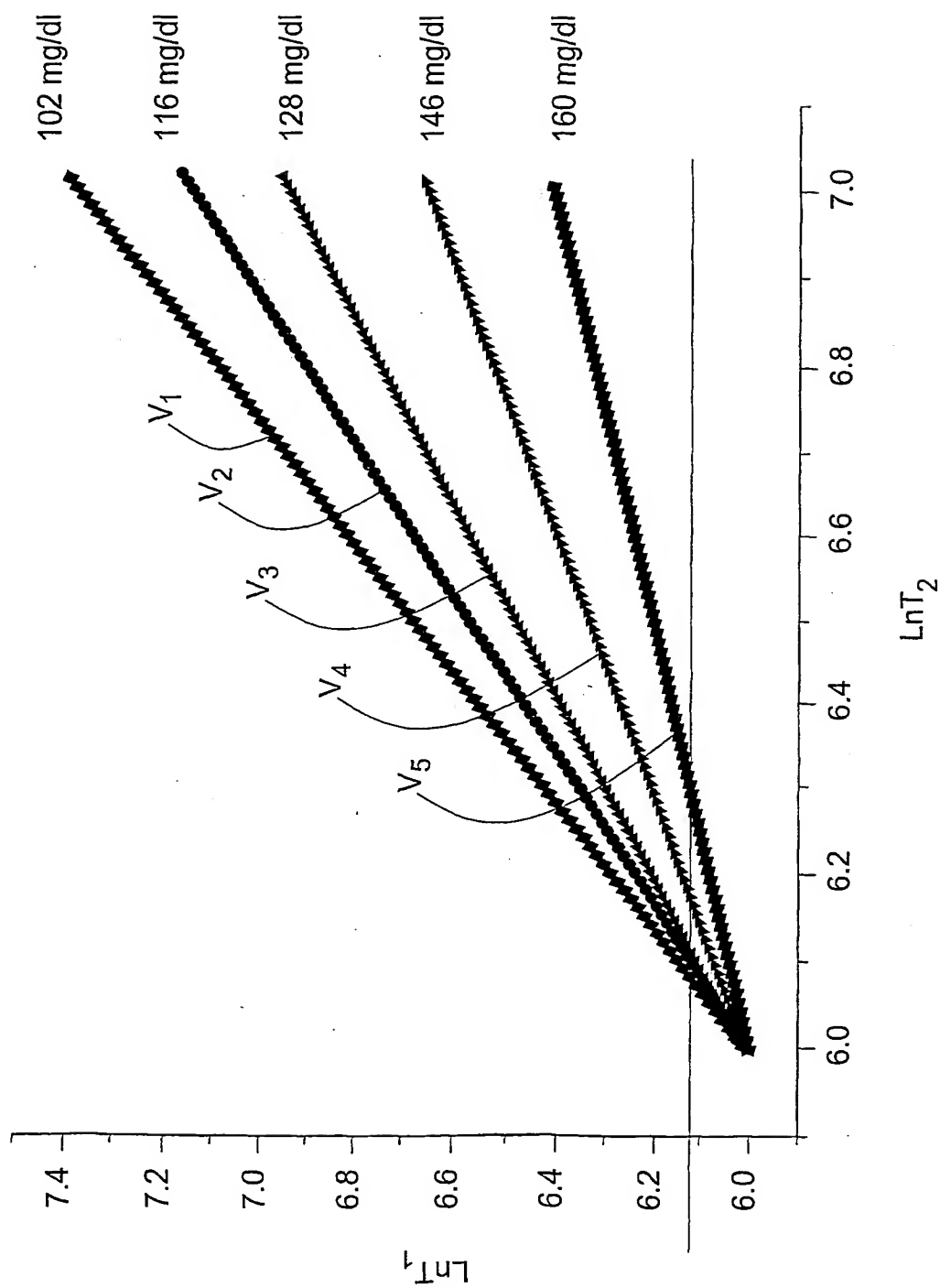


FIG. 5B

10/10

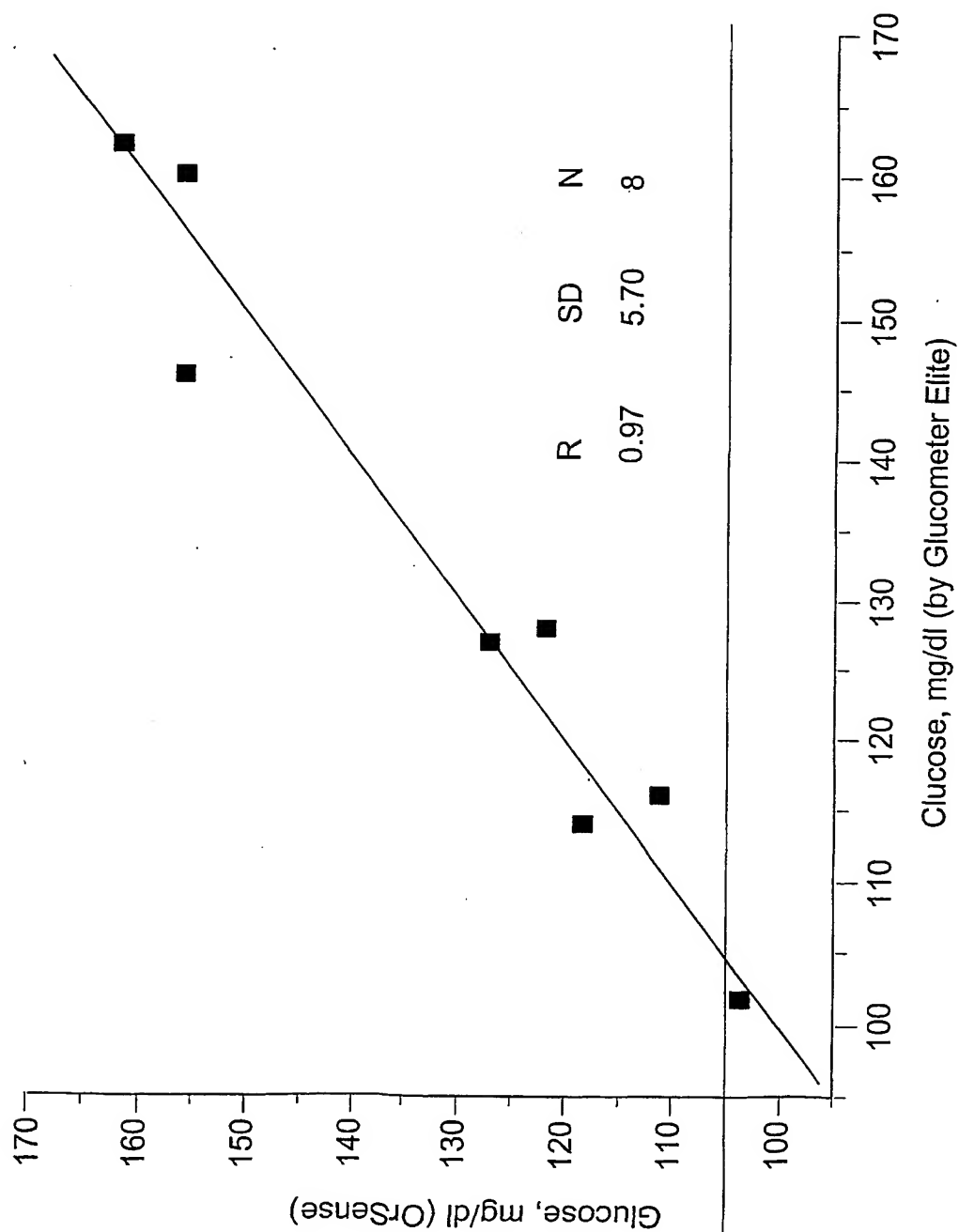


FIG. 7